AN INVESTIGATION

INTO THE

ACTION OF VERATRUM VIRIDE

UPON THE CIRCULATION.

BY H. C. WOOD, JR., M.D.,

ASSISTED BY JOS. BERENS, M.D.*

(*REPRINTED FROM THE PHILADELPHIA MEDICAL TIMES.*)

PART I.—VERATROIDIA.

Section A.—General Action of the Circulation.

AS is well known, some years since I published a physiological paper upon the alkaloids of veratrum viride. This paper, although correct so far as it went, was by no means complete in regard to the therapeutically most important portion of the subject. This lack of completeness arose from two sources. In the first place, the study was my first attempt at this sort of original work, and in the second place, my supply of the alkaloids was exhausted before the investigation was complete. Ever since, I have wished to carry out the work commenced, but have been unable to obtain more

* Dr. Wood took part in all experiments, and is responsible for their accuracy, as well as for the plan of the investigation and all deductions made. Dr. Berens did a full share of the experimental work.

of the alkaloids until recently. As great stress has been laid in a certain quarter upon the fact that the alkaloids which were previously employed were not chemically pure, and as, in some of the experiments hereafter detailed, the poison used certainly was impure, a few words of introduction seem necessary. The researches of Bullock and of Mitchell appear to have positively determined that there are two alkaloids in veratrum viride, and only two. It is a comparatively easy task to separate these alkaloids from each other, but a most difficult if not an impossible one to free completely the separated alkaloids from adherent resin. This resin being inert is a chemical but *not a physiological* impurity, and therefore its presence in greater or less amount only affects the results of experiments in regard to the dose. The alkaloid containing twenty per cent. of resin must, of course, be given in doses twenty per cent. larger than the pure alkaloid, but, this being done, the results are identical. These facts rest upon experimental as well as chemical grounds, the purest alkaloid obtainable having produced, when given in proportionate dose, exactly the same symptoms as were caused by impure specimens.

In my first investigation the following experiments were made to test the action of veratroidia upon the circulation in the uninjured animal.

Experiment I.—(*Exp.* 18.)—A moderate-sized mongrel dog.

TIME.	DOSE.	PULSE.	PRESSURE.	REMARKS.
		108	120–150	Pressure sometimes as low as 110, and as high as 160.
0	gr. 1			Into peritoneal cavity.
5 mi.		106	55–80	Pressure sometimes rises to 95.
7 "				Vomiting. A convulsion.

TIME.	DOSE.	PULSE.	PRESSURE.	REMARKS.
10 m.				Dog apparently dead.
12 "		50	110–150	Several howling, laborious breaths, then quiet. The individual beats of heart very powerful, driving mercury through 40 m.
15 "		140	175–195	The breathing for the last five minutes has consisted of a few paroxysms of half a dozen convulsive respiratory efforts. The pressure has been as high as 210.
16 "		0	0	The mercury fell in the tube almost instantly. Dog dead. The autopsy showed brain and medulla congested with dark blood; right side of heart enormously congested and swollen; left side nearly normal; venous system everywhere gorged; blood very dark.

Experiment II.—(*Exp.* 19.)—Terrier dog.

TIME.	DOSE.	PULSE.	PRESSURE.	REMARKS.
		112	120–160	
0	gr. ½			Hypodermically.
5 m.		112	120–160	
10 "		104	75–90	
15 "		84	75–90	
17 "				Dog vomiting violently.
20 "		68	90–105	Dog still vomiting. No purging or convulsions, but a slight twitching of muscles.
30 "		76	90–105	Some convulsive movements.
35 "			110–120	Dog quiet; not vomiting (hence, probably, arterial pressure increased).
40 "		96	70–90	Immediately after a severe paroxysm of vomiting.
40½ "			90–105	
40¾ "			115–120	Pressure rising sometimes to 125.
41 "			90–105	Directly after a violent opisthotonic convulsion, which has just ceased.
45 "		140	115–120	Dog quiet.
50 "		140	100–115	Rarely rising to 130.

TIME.	DOSE.	PULSE.	PRESSURE.	REMARKS.
53 m.				Dog was unfastened, and pushed off the table; he fell relaxed and stone-like, but in a little while strove to get up, and, struggling violently, slowly progressed forward, scarcely lifting his belly off the ground. Upon being seized a few moments after, he had a violent convulsion, which was quickly followed by total unconsciousness; touching the eyeball producing no effect. Breathing had apparently ceased; pulse very feeble. After lying quiet for some time, he slowly returned to consciousness.
65 "		104	155–175	Dog breathing well again.
80 "		104	95–105	Dog has not moved for fifteen minutes.
	gr. ½			Injected into peritoneum. Dog showing no signs of life when struck or hit.
85 "			80–90	Going up to 100.
90 "				Vomiting.
95 "		108	105–115	
110 "		104	90–100	Dog now untied, and allowed to lie undisturbed. He died in a few minutes.

In commenting upon these experiments I used the following language: "The action of veratroidia upon the heart seems more difficult of interpretation. In Experiment 18 there was a marked depression in the force and rapidity of the blood-movement, lasting for ten minutes. At the end of this time death by asphyxia was rapidly produced, and the circulation underwent a curious change. The pulse, in a moment, was reduced to a minimum in rapidity, but the individual beat became endowed with four times its normal force; the pulse then rapidly rose to one hundred and forty,—twenty beats beyond its pristine number; the individual heart-contractions becoming much more nor-

mal, but the arterial pressure rising far above what it had been previous to the administration of the drug. Then very rapidly the mercury fell, and in a moment the heart was stopped, and all was over.

"I think the most probable explanation of this curious phenomenon is to be looked for in the sudden cessation of the respiration, and the consequent rapid production of asphyxia. The increase in the force and rapidity of the heart's action was most probably due to the overpowering of the specific action of the veratroidia by that of the carbonized blood. In his admirable 'Physiological, Pathological, and Anatomical Researches' (p. 33), Dr. Reid has a paper on the 'Phenomena of Asphyxia,' from which the following is extracted:

"'When the animal was breathing freely through the tube in the trachea, was quiescent, and when the blood was fully arterialized, the range of level in the mercury in the tube seldom exceeded half an inch, sometimes not so much. When the stopcock was shut, no change took place in the range of the mercury during the first half-minute; generally before the end of the first minute the animal had begun to struggle, and the range greatly increased, rising during each attempt at expiration, and during the struggling of the animal. In some experiments the range of mercury amounted to about nine inches, and in one experiment to ten inches.

"'In a third experiment, the pulse was 100 before the stopcock was turned; at the end of one minute the blood was getting dark, the animal was beginning to struggle, and the pulse was 120. During the second minute the animal struggled violently, and the pulse could not be reckoned. At the end of two and a half minutes the animal

ceased to struggle, the respirations were few and heaving, and the pulse was 78.'

"In Experiment 19, the primary period of depression ended in a gradual increase in the frequency and force of the pulse, which had risen to 140 instead of 112 in a minute,—the number before its administration,—but had not quite regained the force which it had had previous to the use of the drug, when a period of collapse and apparent death came on; after reaction from this, however, the circulation more than regained the power which it had at first. A further dose of the veratroidia was followed by the same depression and subsequent rebound of the circulation. The indications do not, in this case, point so clearly to the accumulating carbonic acid as the cause of the secondary arterial excitement, but I cannot help believing it has something to do with the latter."

In the present investigation, the first experiments with veratroidia were directed to discovering whether the effects obtained in the study of Mr. Bullock's alkaloid are constant. These experiments are as follows:

Experiment III.—Small stout dog.

TIME.	DOSE.	PULSE.	PRESSURE.	REMARKS.
		140	110–115	Respiratory efforts frequent and deep, during which a maximum and minimum pressure was attained of 100–125.
0	gr. 1-40			Injected into femoral vein.
10 sec.			10	
30 "			0	
45 "				Pressure rising; the respiration profoundly affected; vomiting.
1 m.			140	
1¼ "			165	Respiration ceased; the pulse very weak and quivering; blood very black.
1¾ "				Respiration resumed.

TIME.	DOSE.	PULSE.	PRESSURE.	REMARKS.
2 m.			10	
3 "		114		Pulse very weak. *Clot.*
6 "		198	200	Pressure has been up to 210. *Clot.*
7 "				
11 "			115–130	Pressure sometimes falling as low as 100, and rising to 145. The respiratory efforts three in a minute, and shallow and gasping in character.
12 "		100	90–110	Individual beat fifteen cent. Respirations but two to the minute.
21 "		84	80–85	Respirations but *one* to the minute.
21¾ "	gr. 1-40			Into femoral vein. The pressure fell instantly.
21¾ "			40	
22¾ "			85	
23¾ "			110–120	
26 "		165	95–100	Pressure rising to 115 and falling to 90. Respiration feeble and slow.
35 "	gr. 3-40			Heart instantly arrested. The organ was flabby; responded feebly to stimuli, and filled with black blood.

NOTE.—Some blood drawn from the femoral artery just previous to death was found exceedingly black and venous in character, but rapidly changed to a bright arterial hue after a few moments' exposure to the air.

Experiment IV.—Moderate-sized dog.

TIME.	DOSE.	PULSE.	PRESSURE.	TEMP.	REMARKS.
		150	115–125	103½°	Breathing regular. Pressure sometimes falling to 100, and during strong respiratory effort rises to 145.
0	gr. 1-20				Injected subcutaneously.
7 m.				102½°	Respiration begins to be affected.
17 "		60	50–75	102¼°	Individual beat 25 cent. Respirations deep; nine to the minute.
27 "		42	48–65	101¾°	

TIME.	DOSE.	PULSE.	PRESSURE.	TEMP.	REMARKS.
28 m.			25–40	100¾°	Efforts at vomiting.
30 "			105–135		Dog has just vomited.
30¼ "			125–150		
30½ "			130–160		Vomiting ceased.
31 "			90–115		Respiration almost ceased. Pressure has been lower.
32½ "					Respirations irregular; four to the minute.
34 "		36	60–95	100¼°	Clot. The tube inserted in vessel on opposite side.
38½ "				99¾°	
43 "			50–60	99½°	There is violent purging. Stools liquid and greenish. Arterial blood very black, and clots easily.
53 "		50	35–75	98½°	Breathing very slow. Pulse irregular. During respiratory effort pulse and pressure both rise, falling again in the respiratory interval.
58 "	gr. 1-20				
62 "				97°	Blood very dark. Injection has had little apparent effect.
63 "	gr. 3-20				In peritoneal cavity.
88 "					No marked effect.
89 "	gr. 3-20				In peritoneal cavity.
91 "					Violent vomiting of greenish fluid. Breathing very rapid and irregular.
91½ "					Respirations slow and labored; dog struggling violently for breath. Blood drawn from femoral artery very black, but becomes bright red after exposure to air.
96 "					Dog dead. Heart large and flabby, but filled with dark blood. Alimentary canal much inflamed throughout.

Experiment V.—A very stout, large terrier.

TIME.	DOSE.	PULSE.	PRESSURE.	REMARKS.
		120	110–120	
0	gr. 1-40			All or nearly all of this dose was lost in attempting to inject into the femoral vein.
5 m.				
9 "		120	115–122	
11½ "		144	117–123	
13 "			115–123	
16 "			120–125	
17½ "	gr. 1-40			Injected into femoral vein.
18½ "			10–15	Respiration exceedingly affected; very labored.
18¾ "			85–110	Vomiting freely.
19½ "			95–120	Respiration almost arrested.
20 "			135	Arterial blood perfectly black.
21 "			180	Deep respiration; paroxysms at very long intervals.
22 "			245	
23 "		18	160	Decided change in color of blood. Respiration becoming more frequent.
25¼ "			90–100	
26 "		54	70–90	
27 "			65–97	Respiration in paroxysms at long intervals. During intervals pressure falls to 60–70, but rises to 60–100 after inspiratory efforts.
30½ "			68–80	Cut one pneumogastric.
32 "			130	
32½ "			95–105	
34 "			90–100	
34½ "			80–87	
35 "			95–100	Respiration very weak.
35½ "			115–122	Cut remaining pneumogastric.
36 "			110–115	
37½ "			68–73	
52 "			40–43	Into femoral vein.
52½ "	gr. 1-40		35–40	
52¾ "			40–45	Respiration very labored.
54 "			65–70	Injected into femoral vein.
54½ "	gr. 1-40		75–80	
55 "			90–95	Efforts at vomiting.
59 "			95–100	Pulse very rapid. Arterial blood very black.
63 "				Vomiting of a large quantity of mucus of deep greenish tint —probably due to bile.

A careful study of these experiments will show their complete agreement with those of my previous

study. In Experiment III., the blood-pressure, after the first injection into the vein, fell to zero in the course of thirty seconds, and in one and a quarter minutes had risen again to 165,—the original point having been 110; and similar phenomena were also witnessed after subsequent injections. In Experiment IV., the alkaloid was thrown not into a vein, but into the cellular tissue, and the succession of phenomena was therefore less rapid, and, accordingly, in closer accord with what occurred in the trials with Bullock's preparation. Seventeen minutes after the injection the pressure was about one-half what it was originally, whilst thirteen minutes later it was more than one-fifth greater than normal,—a fall of one-half, a rise of one-fifth.

In Experiment V., the alkaloid was thrown directly into the circulation, and in one and a half minutes the pressure, which had been 120, was down to 10, but in three minutes had risen to 245. It is very plain that the fall and rise not only take place much more quickly when the drug is thrown directly into the veins, but are also much exaggerated. This fact would seem to indicate that the primary fall is due to a direct action of the alkaloid upon the heart or its nerve-supply, whilst the secondary rise has its source in some indirect action of the poison. A reference to the record of Experiment III. or of Experiment V. will show that the alkaloid produces an intense disturbance of the respiration, and that the secondary rise of the arterial pressure was simultaneous with, and proportionate to, this disturbance. In my previous article the great probability that the rise was simply due to the excess of carbonic acid in the blood was fully shown, and the remarks thereon have already been quoted. In order to test absolutely the matter, the alkaloid was administered, and forcible artificial respiration was

kept up. Under these circumstances, as will be seen from the following records, the secondary rise of the mercury in the manometer was altogether prevented, the arterial pressure being steadily depressed. If the bellows were kept quiet for an instant, however, and the animal left to its own unaided powers, the blood commenced to grow dark, and the pressure to rise, only to fall at once when the artificial respiration was again resorted to. In experiments hereafter detailed, these results were repeatedly confirmed; and, although at times other results seemed to be achieved, it was always found that a leak in the bellows or some other accident or circumstance had interfered with the efficiency of the artificial respiration. The experiments are as follows:

Experiment VI.—A stout dog of medium size.

TIME.	DOSE.	PULSE.	PRESSURE.	REMARKS.
		100	100–110	Grain one-sixth of woorari injected into femoral vein, and artificial respiration practised.
0	gr. 1-40			Into femoral vein.
1-10 m.			15	
½ "		102	80	Slight vomiting, efforts interfering somewhat with artificial respiration.
2¼ "			100–110	
3 "			80–100	
8 "			30–45	Individual beat 13 cent. Arterial blood bright scarlet.
14 "		52		
17 "		60	30–45	

Experiment VII.—A stout young pup.

TIME.	DOSE.	PULSE.	PRESSURE.	REMARKS.
		130	90–100	
0 m.	gr. 1-40			Into femoral vein. Artificial respiration.
1-10 "				Pressure was falling rapidly, when the blood clotted in the tube.

TIME.	DOSE.	PULSE.	PRESSURE.	REMARKS.
3 m.			80–85	
6 "			75–80	
15 "			45–50	
16 "			50	
23 "			40–45	

Experiment VIII.—A moderate-sized dog.

TIME.	DOSE.	PULSE.	PRESSURE.	REMARKS.
		90	115–125	Artificial respiration applied very actively.
0 m.	gr. 1-50		130–135	Injected into the femoral vein.
½ "			65–75	
1 "		44	60–75	
2 "			80–95	
4 "		60	80–105	
5 "			90–110	
6 "		60	95–110	
8 "		93	90–110	
10 "		90	85–95	
11½ "	gr. 1-40			Into femoral vein.
11¾ "				After injection, pressure fell at once to 70, but a clot prevented further observation of the fall.
18 "			50–58	
19 "		88	50–58	

As a contrast to these experiments, and as showing the influence an excess of carbonic acid in the blood has over the depression of the arterial pressure caused by veratroidia, the following experiment is recorded. Although thus reported separately, for obvious reasons, it was in truth a continuation of Experiment VII.

Experiment IX.—A stout young pup.

TIME.	DOSE.	PRESSURE.	REMARKS.
0 m.	gr. 1-40		Into femoral vein.
23 "		40–45	Cut pneumogastrics.
52 "	gr. 1-40	50–60	Into femoral vein. Artificial respiration suspended.
55 "		135	
56 "		145–170	
56½ "		210	Dog making violent respiratory efforts.
61 "		130–135	Blood black. Artificial respiration resumed.
61¼ "		55–60	

Section B.—Action on the Heart and its Nerves.

It having been determined that the direct action of veratroidia upon the circulation is to lower the arterial pressure, and at the same time to slow the pulse, the question naturally arose, Does the alkaloid act directly upon the heart, or does it influence the latter slowly through the nervous centres? The following experiments were instituted to settle this point:

Experiment X.—A stout tomcat. During anæsthesia, opened the ascending cava and injected three-fourths of a grain of veratroidia (impure). There was an instantaneous arrest of respiration, followed at once by a violent general tetanic spasm, involving all the muscular system and the diaphragm. After the injection, the heart beat several times quite forcibly, though not nearly with the normal strength. Upon opening the thorax, the heart was found making vermicular contractions, which continued for some minutes. The venous pressure in the large veins was very decided, causing the blood to squirt from them when cut.

Experiment XI.—A large dog. One-tenth of a grain of pure veratroidia was injected into the femoral vein. The heart was immediately arrested in diastole, and, respiration occurring, became enormously dilated with blood. The auricles continued to pulsate. The left

ventricle contained arterial blood, the right venous blood. The application of the strongest current to the surface of the heart, or by needles introduced into it, induced no contractions whatever.

Experiment XII.—A large cat. The spine was cut in the upper dorsal region, and a small hole was made in the chest, so that the finger could be inserted in such a way as to rest on the heart,—the animal being kept during the entire period anæsthetized. One-eightieth of a grain of veratroidia (impure) was injected into the femoral vein, without any very obvious effect. One-fortieth of a grain was then injected, with a similarly negative result. One-half of a grain was finally thrown into the vein, and the heart-beats at once commenced to slacken, and soon ceased. At the immediate autopsy the heart was found to be flabby and dilated. It refused entirely to respond to galvanic currents.

Experiment XIII.—A large terrier cur had his cord cut in the extreme upper dorsal or lower cervical region, and the par vagum also divided. The respiration was maintained artificially. The animal received various small doses of impure veratroidia, and finally one-fourth of a grain was thrown at once into the femoral vein. In a minute, or less, the pressure fell to nothing, and pulsations ceased. At the immediate autopsy the heart was found flabby and dilated. Galvanic currents had no perceptible effect upon it.

Experiment XIV.—A large cur dog had its cord cut in the upper dorsal (lower cervical?) region, and afterwards its pneumogastrics. After small amounts of a very impure veratroidia had been exhibited, three half-grain injections were thrown, in as many minutes, into the femoral vein. The heart-movements ceased immediately after the last injection; the pressure in half a minute fell to ten, in another half-minute to zero. The strongest currents were unable to affect the cardiac muscle.

The above experiments, which have been confirmed at various times, certainly prove that veratroidia has a direct action upon the cardiac muscle: of course, those made after previous division of the

cord and of the pneumogastrics, *i.e.*, after isolation of the heart, are the most satisfactory. In Experiment X. there is indeed no proof that the arrest was really the result of a direct action of the poison upon the cardiac muscle.

A fact which is indicated by the above experiments, and which is very obvious in the light of subsequent experimentation, is that very large doses of the alkaloid are required to affect the cardiac muscle,—doses much greater than are sufficient to kill, and very much greater than the minimum amount which will profoundly affect the respiration. It seemed probable, and subsequent experimentation has confirmed the surmise, that the drug has some action upon the heart besides that which it exerts directly on the cardiac muscle. In endeavoring to determine this, the first study was as to its influence upon the cardiac inhibitory nerves.

A reference to Experiment IV. or V. will show that an enormous reduction of the pulse follows the exhibition of veratroidia. Experiment further shows that this occurs when artificial respiration is kept up actively, and therefore that it is due not to an indirect action of the alkaloid, but to an influence exerted directly on the heart or its nerves. The reduction in the number of the pulse-rate may be due to an influence exerted upon the pneumogastrics, or may be the result of some other cause. To test this, the following experiments were undertaken:

Experiment XV.—A stout terrier. A small dose of woorari, just enough to quiet, given, and artificial respiration practised.

TIME.	DOSE.	PULSE.	REMARKS.
0 m.			Cut the pneumogastrics.
27 "		168	
30 "	gr. 1-40		Injected into the peritoneal cavity.
30 "	gr. 1-40		Injected into the peritoneal cavity.
47 "		189	

Experiment XVI.—A stout cur.

TIME.	DOSE.	PULSE.	REMARKS.
0 m.			Cut the pneumogastrics.
26 "		176	
64 "		180	
76 "	gr. 1-40		
78 "	gr. 1-40		
82 "		164	
90 "	gr. 1-40	168	
104 "		212	
110 "	gr. 1-20	112	
113 "		204	

These two experiments are in accord in showing that doses of the drug which, in the uninjured dog, lower the pulse-rate very greatly, have no effect when the par vagum has been previously divided. Proof is thus afforded that the reduction of the pulse which is ordinarily present is brought about through the inhibitory nerves. Another method of getting the same result is by a division of the par vagum in the animal under the influence of the poison, as in the following experiments:

Experiment XVII.—A stout dog.

TIME.	DOSE.	PULSE.	REMARKS.
0 m.		68	
1 "	gr. 1-40		Injected into the carotid slowly.
3 "		44	
11 "		52	
12 "			Cut the pneumogastrics.
12¼ "		168	

This experiment is in accord with those previously given, and seems, with them, to establish the fact that the primary slowing of the cardiac beats by the drug is chiefly brought about by an action on the inhibitory cardiac nerves.

This being so, it is *a priori* to be expected that when the heart is freed from the influence of all the nerves antagonistic to the pneumogastrics, the results of the primary inhibitory impression should be very marked.

In order to test this point, the following experiments were performed:

Experiment XVIII.—A large cur dog. Veratroidia impure. The spine was cut in the lower cervical region.

TIME.	DOSE.	PULSE.	PRESSURE.	REMARKS.
0 m.		136	85–93	
3 "		122	35–40	The fall is due to an extremely active artificial respiration.
8 "				Artificial respiration regulated to thirty strokes of bellows per minute, and so kept during the rest of the experiment.
13 "		160	65–70	
14 "	gr. 1-30		65–70	One-thirtieth grain injected into femoral vein. Instantly the arterial pressure fell nearly to zero, and all movement ceased. No pulse could be felt in the exposed carotids or femorals, or motion of the heart through the chest-walls. About one minute after this, the pneumogastrics were cut, and instantly the pulse returned in the carotids and femorals.
31 "		168	50–60	

Experiment XIX.—A youngish cur, of moderate size. The cord was cut in the extreme upper dorsal or lower cervical region. After some time, one-fortieth of a grain of impure veratroidia was injected into the femoral vein. Before this, the mercury in the cardiometer had shown signs of the formation of a clot, but instantly after the injection the mercury fell very much, and after one or two very slow pulsations all movement ceased. The pneumogastrics were divided, but a clot prevented any movement of the mercury. On opening the chest, the heart was found to be in vigorous movement.

Experiment XX.—A powerful bull-dog.

TIME.	DOSE.	PULSE.	PRESSURE.	REMARKS.
0 m.				Spine cut in lower cervical region.
23 "			95–105	Artificial respiration.
26 "		56	90–100	
32 "		56		
38 "			90–105	
45 "	gr. 1-12			One-twelfth grain injected into the femoral vein. The mercury fell at once to 10 (equivalent to zero). No beat occurred for one or two seconds, then a succession of very distant, slow, and powerful beats, with a great rise of arterial pressure, followed by a greatly increased rapidity of heart's action. In a few seconds this high pressure gave way to a sudden slowing or stoppage of the pulse and fall of the pressure to 15; then slow, distant, very full beats (15 c. each), followed by a rise of pressure to 125, with a rapid pulse, then another fall, etc., as before.
49 "				Alternations continuing, but not so marked as before.
51½ "	gr. 1-12		95–100	Injected as before.
51¾ "			20–35	
52 "			145–160	
52¼ "			30–33	
52⅓ "			140–145	
52½ "			50–60	
53 "				Same alternation of rise and fall.
54 "	gr. ⅓			Into jugular.
61 "			55–60	
62½ "	gr. ⅓			Into jugular.
64 "		180	80–180	
70 "		168	40–50	There is no longer a marked rise or fall of the mercury or pulse. Both have been very steady at their present position for some minutes.
70½ "				Par vagum cut.
71½ "		168	55–60	
73 "			55–60	
79 "		168	50–60	Dog killed.

These experiments certainly are corroborative of the conclusions previously reached, namely, that the

primary slowing of the pulse by veratroidia is due to a stimulant effect upon the inhibitory nerves. The vaso-motor nervous system having been paralyzed, and possibly the accelerators of the heart also, by the spinal section, full sway was left to the inhibitory nerves, and consequently in Experiment XVIII., where a minute dose of the alkaloid was thrown into the circulation, there was immediate diastolic arrest, and the singular phenomenon was offered of a heart, quiet, dilated, and seemingly dead, started into new life by division of the pneumogastric nerves,—*i.e.*, by removal of the inhibitory influence. The strength of the inhibitory apparatus is known to vary very much even in different individuals of the same species, and the diverse results reached in the last and the first of these experiments are merely instances of difference in degree and not in kind. The extraordinary rise and fall of the mercury in the cardiometer-tube, the incessant succession of cycles of diastolic cardiac arrest, prolongations of the beat, and hurried action of the heart, are explainable only upon the supposition that the inhibitory apparatus was intensely excited, but was unable to hold, as it were, the normal cardiac impulse completely in its power. The rapid alternations were, in other words, merely the varying phases of a struggle between the two forces or powers.

Upon examining the record of this last experiment, it will be seen that after the injection of a large dose of the alkaloid the alternations of low and high pressure ceased, and the mercury in the manometer became steady at a position much below normal. The most plausible explanation of this is that the excess of the poison changed a condition of inhibitory excitation into one of inhibitory paralysis, or, in other words, that whilst a small dose of veratroidia excites, a large one paralyzes the pneumogastrics.

This explanation is strongly confirmed by the fact that coincident with the settling down of the pressure in the experiment just alluded to, there was a rise in the number of the pulse, and that section of the par vagum at this time did not affect the pulse-rate; a proof that the pneumogastrics were really paralyzed.

In order, however, to establish beyond peradventure the truth of the proposition, the following experiments were performed:

Experiment XXI.—A very small dog.

TIME.	DOSE.	REMARKS.
0 m.	gr. 1-40	Into femoral vein.
11 "	gr. 1-40	" "
29 "	gr. 1-20	" "
43 "	gr. 1-20	
46 "		A current was applied to the pneumogastrics (just cut), at first mild, afterwards very intense; no effect whatever was induced; the nerve was completely paralyzed.

Experiment XXII.—A young, stout pup.

TIME.	DOSE.	PULSE.	PRESSURE.	REMARKS.
0 m.	gr. 1-40	130	90–100	Into femoral vein.
25 "				Cut pneumogastrics.
25½ "		165	45–50	
28 "				Current to par vagum affected the heart very much.
32 "	gr. 1-40		30–35	Into femoral vein.
34½ "		192		
35 "				Applied strong current to par vagum; no effect.
38 "		186	80–85	
40 "				Very strong current to par vagum.
40½ "		186	45–50	Current broken.
44 "			45–50	
65 "		186	38–52	Current applied to pneumogastrics in the root of the neck where they had not been previously touched; no effect.

Experiment XXIII.—A stout terrier. Artificial respiration and small dose of woorari, just enough to quiet.

TIME.	DOSE.	PULSE.	PRESSURE.	REMARKS.
0 m.			85–95	
15 "			85–95	Cut pneumogastrics.
21 "				Current applied to pneumogastrics caused instant fall of pressure and prolonged diastolic arrest.
21½ "			15	
27 "		168	45–50	
30 "	gr. 1-40		65–75	Injected into the peritoneal cavity.
39 "	gr. 1-40		60–70	Injected as before.
47 "		189		
48 "			15	Application of current as before caused diastolic arrest and fall.
53 "	gr. 1-40		45–55	Into femoral vein.
61 "			20	Some fall under application of current to par vagum and slowing of pulse, but no diastolic arrest.
65 "			30–35	
68 "				A very intense current applied to the pneumogastrics failed to influence the heart.

Experiment XXIV.

TIME.	DOSE.	PULSE.	PRESSURE.	REMARKS.
				Artificial respiration resorted to, with exhibition of woorari in dose sufficient to keep the dog quiet.
0 m.	gr. 1-20		*15½–16	Injected into peritoneal cavity.
6 "			10½–11	
10 "				Pneumogastrics cut. Canula changed to carotid artery.
20 "			10–12	
38 "			9–11	Under a strong current passed through the pneumogastrics, which also slowed action of heart.

* In this experiment there was used a cardiometer with larger divisions of the scale than the one commonly employed.

TIME.	DOSE.	PULSE.	PRESSURE.	REMARKS.
68 m.	gr. 1-10			Into peritoneal cavity.
90 "			9	Current applied to pneumogastrics had no effect whatever.
				The arterial blood throughout this experiment was very dark and venous in appearance, owing to a leak in the bellows.

Experiment XXV.—A stout cur.

TIME.	DOSE.	PULSE.	PRESSURE.	REMARKS.
0 m.				Par vagum cut.
26 "		176	140–145	
48 "		0	0	Instant diastolic arrest from mild current to par vagum.
50 "	gr. 1-40			Into femoral vein.
52 "	gr. 1-20			Doubtful how much of these injections entered; some obstruction in the canula.
58 "		164	100–105	
64 "	gr. 1-20	168	110–115	Into femoral vein.
75 "			85–90	Began artificial respiration.
84 "	gr. 1-20	112	80–85	Into femoral vein.
91 "				Current of same strength as before to par vagum; at first no effect.
93 "		52	50–60	Current continued.
93¼ "				Current broken.
97 "	gr. 1-20	84	75–80	
99 "		80	50–60	Very intense current applied to a freshly exposed portion of the pneumogastrics, low down in the neck, had no effect whatever.

These experiments speak so plainly for themselves that a discussion of them is scarcely necessary. They are five in number, and in each case it will be noticed that after a full dose of the poison even the most intense faradaic currents applied to the pneumogastrics failed to affect the heart. Every precaution was taken to prevent the possible fallacy of an exhaustion of the nerve by the current itself,

and the teachings of the experiments must be received as final. It would have been very well to have tested the comparative sensibility of the par vagum before and after the injection of small doses of the poison, and thereby to have determined whether the inhibitory excitement primarily induced by such doses of the alkaloid is centric or peripheral. The doing of this, however, would have required an accurate determination of the minimum power of current required in the unpoisoned animal to influence the heart, and such determination necessitates the use of more delicate apparatus than was at hand. The final inhibitory paralysis is certainly peripheral; but whether the primary inhibitory stimulation is centric or peripheral must be left for other investigations to determine.

Section C.—Action on the Vaso-Motor System.

From the evidence which has already been brought forward, it is very plain that veratroidia exerts a powerful influence upon the heart and its nerve-supply. The question as to its influence upon the vaso-motor nervous system is a separate one, but its answer is rendered more difficult by the cardiac action of the drug. There are evidently three or four sets of experiments, by the comparison of whose results light may be thrown upon the vaso-motor action of the alkaloid. First, experiments in which the drug is given to the uninjured animal, artificial respiration being maintained to avoid the influence of the altered breathing; second, experiments in which the heart is separated from the inhibitory centres; third, those in which vaso-motor paralysis is induced by section of the spine; fourth, those in which both the pneumogastrics and spine are cut.

To the first of these classes belong Experiments

V., VI., and VII. A reference to them will show that the arterial pressure falls very decidedly under the influence of the drug. The mere reduction in the number of the pulse will in a measure account for this fall, but on examining closely the record of Experiment VII. it will be noticed that although the pulse was at first greatly reduced in number, yet afterwards the rate of the cardiac pulsations rose nearly to the pristine point, although the pressure was a good deal less than half what it was originally. The conclusion is logically inevitable that in large amounts veratroidia either weakens the cardiac muscles, or produces vaso-motor paralysis, or does both. In regard to its action in small doses, these experiments bear no evidence.

In order to decide the influence of the drug upon the arterial pressure after division of the pneumogastrics, the following experiments were instituted:

Experiment XXVI.—A stout terrier. Artificial respiration; woorari in just sufficient quantity to quiet.

TIME.	DOSE.	PRESSURE.	REMARKS.
0 m.		85–95	
15 "		85–95	Cut the pneumogastrics.
16 "		120–130	
30 "	gr. 1-40	65–75	Injected into the peritoneal cavity.
34 "		65–75	
39 "	gr. 1-40	60–70	Injected into the peritoneal cavity.
53 "	gr. 1-40	45–55	Injected into the femoral vein.
53⅚ "		30	
54 "		50–60	
60 "		35–40	
65 "		30–35	

Experiment XXVII.—A stout cur. Pneumogastrics cut twenty-six minutes before the first note.

TIME.	DOSE.	PRESSURE.	REMARKS.
0 m.		140–145	
3 "		145–150	
5 "		140–145	
39 "		137–140	
50 "	gr. 1-40		Injected into femoral vein.
52 "	gr. 1-20		Injected in vein. Owing to an accident, doubtful how much of these two injections entered the circulation.
56 "		100–105	
59 "		110–112	
64 "	gr. 1-20	110–115	Into femoral vein.
78 "		120–140	Artificial respiration imperfect.
79½ "		75–85	Artificial respiration very active.
80½ "		90–95	
81½ "		50–60	
82 "		90–95	Artificial respiration imperfect.
82½ "			Artificial respiration ceased.
83 "		170–175	Artificial respiration renewed.
83½ "		100–103	
84 "		80–85	

These two experiments certainly show that, in full dose, veratroidia is capable of lowering the arterial pressure after section of the pneumogastrics, and also that small doses have but very slight effect under these circumstances.

Experiment XXVII. shows that this depression of the circulation is not due to actual paralysis. For at the eighty-second minute, when the arterial pressure was less than two-thirds its original amount, the carbonic acid which accumulated in the half-minute during which artificial respiration was interrupted was able nearly to double the pressure, driving the mercury far above its original point. This fact seems to indicate that the fall of pressure was not due to a vaso-motor paralysis, but to a sedative action on the cardiac muscle,—a sedative action which was soon overcome by the intense stimulation of the carbonic acid. Be this

as it may, it is evident that if the fall of pressure be due solely to vaso-motor paralysis, it ought not to occur after division of the cord. To test this, the following experiments were performed:

Experiment XXVIII.—Dog.

TIME.	DOSE.	PULSE.	PRESSURE.	REMARKS.
				Spine cut in upper dorsal region. Artificial respiration applied.
0 m.		116	90–105	This is twenty-two minutes after cutting the spine.
6 "		120	75–80	Under more active artificial respiration.
8 "			95–100	Less active artificial respiration.
9 "			80–85	Pneumogastrics cut.
12 "		120	65–70	
14 "			75–80	A current, at first mild and then intense, applied to freshly-exposed crural nerve, for a minute and a half. No effect on the arterial pressure.
20 "		112	65–75	
26 "	gr. 1-20	118	60–65	Into femoral vein.
27 "			45–55	
28 "	gr. 1-20	120	55–65	Pressure sometimes rising to seventy. It is not certain how much of these last two injections reached the circulation.
31 "		120	45–65	
32 "		100	40–45	Under very active artificial respiration.
33 "		100	45–50	
35 "			45–50	
38 "		108	35–40	
43 "		116		The tube has been put into carotid.
44 "		120	25–30	
46 "			210	Under galvanic current applied to the spine. There was a general intense spasm of all the muscles, but the pressure did not fall at once, when the current was broken, and the muscles became relaxed.
47¼ "		200	180	A minute has elapsed since current was taken off.
47¾ "			110–115	
49 "			170	Caused by the passage of a current through the body of the dog, producing violent muscular spasms. The pressure fell instantly when current was broken. This was repeated several times, with same result.

Experiment XXIX.—A large terrier cur. Cord cut in extreme upper dorsal region.

TIME.	DOSE.	PULSE.	PRESSURE.	REMARKS.
0 m.				Par vagum cut.
12 "		176	85–90	
13 "	gr. 1-10			Injected into femoral vein. Artificial respiration.
14 "			65–75	
16 "		170	60–70	
22 "	gr. 1-10		50–60	Into femoral vein.
23 "			55–65	
24 "			55–70	
31 "		176	45–48	
40 "		174	40–43	
45 "	gr. 1-10		30–35	Into femoral vein.
46 "		176	30–35	
47½ "		176	35–40	
56 "		176	40–41	
58 "			30–35	
65 "			60–65	
65½ "	gr. ⅙			Into jugular. Dropped a few seconds after injection to fifty at one bound, and rose again to seventy.
69 "	gr. ⅙		90–105	Into jugular. Fell as before to sixty.
70 "		200	60–65	
72 "			70–75	
73 "		184	85–90	Another injection of one-fourth grain into jugular was followed by a fall of the arterial pressure to nothing and cessation of pulsation. The heart refused to react to galvanism.

Experiment XXX.—A large cur dog. Veratroidia impure. Spine cut in the lower cervical or extreme upper dorsal region.

TIME.	DOSE.	PULSE.	PRESSURE.	REMARKS.
0 m.		136	85–93	
14 "	gr. 1-30		65–70	Injected into femoral vein.
28 "				Par vagum cut.
31 "	gr. 1-10	168	50–60	Into femoral vein.
34 "		162	50–60	
36 "			45–50	Lost some blood.
47 "	gr. 1-10	152	30–35	Into femoral vein.
48 "		128	30–35	
60 "		160	30–35	

TIME.	DOSE.	PULSE.	PRESSURE.	REMARKS.
61 m.	gr. 1		30–35	
61½ "			50–55	
63 "		172	70–75, going to 80.	
64 "			75–85	
65 "		188	65–75	
66 "			65–70	
67 "	gr. ½			Into femoral.
68 "			55–65	
69 "	gr. ½	186	55–65	
69½ "			30–35	
70 "	gr. ½			
70½ "			50–55	Mercury then dropped at once to zero. The heart immediately afterwards at the autopsy was found incapable of responding to stimuli.

In studying these experiments, it will be perceived that in the first the arterial pressure under the influence of the poison fell very steadily and very decidedly up to the time when galvanism was applied to the spine, and the experiment, so far as it affects the point now under discussion, was ended. The second and third of these experiments (XXIX., XXX.) are in accord in that the pressure for a long time fell with sufficient regularity, but after the exhibition of enormous doses of the drug rose again, the rise being in each instance coincident with an increase in the pulse-rate. The explanation of this phenomenon is difficult. Any defect in the artificial respiration will, under the circumstances present in the experiments, give rise to an increased arterial pressure, and the increase which occurred may possibly have had such origin. The probabilities would seem to be, however, that the secondary rise of pressure was really caused by the drug. As the exact position at which the spine was divided was, unfortunately, not noted, it is barely possible that the point of section was below the position at

which the accelerators of the heart are given off, and that the increased pulse-rate was due to a stimulation of these accelerators, the increased pressure being the result of the increased frequency of the heart-beats. Be these things as they may, it is certainly a fair deduction from the record—first, that the fall of pressure produced by veratroidia is not caused solely by its vaso-motor action; and second, that a study of the arterial pressure indicates that when used in moderate doses the alkaloid has very little influence upon the vaso-motor nervous system. In order, however, to test this matter more accurately, other experiments have been performed. It is well known that when a sensitive nerve or even a portion of the skin is irritated in the rabbit, a very great rise of arterial pressure is produced. In the dog the result is less constant, and in some cases the pressure even falls. The cause of this is the very great power and sensitiveness of the cardiac inhibitory nerves in the dog, for as the result of this sensitiveness and power the heart is depressed so much by the pain as more or less to overbalance the effect of the vaso-motor spasm. This is shown by the fact that the rise of pressure is very marked when an afferent nerve is irritated *after* section of the pneumogastrics. The fact (see Exp. XXVIII.) that after section of the cord stimulation of a nerve is powerless to cause rise of pressure, shows that the latter is due to a vaso-motor spasm, and that the vaso-motor centres are placed above the cord.

In order to test the influence of veratroidia upon the vaso-motor centres, the following experiments in conformity with the above-mentioned facts were performed:

Experiment XXXI.—A stout bull-terrier pup.

TIME.	DOSE.	PRESSURE.	REMARKS.
0 m.	gr. 1-40		Injected into femoral vein.
25 "			Cut the pneumogastrics.
29 "			
30 "		35–40	
30¼ "		50–55	Rise due to momentary application of a mild current to crural nerve.
31 "		30–35	
32 "	gr. 1-40	30–35	Injected into femoral vein.
46 "		35–40	
47 "			Strong current applied to a freshly-dissected crural nerve.
48 "		110	Current broken.
49 "		35–40	
71 "	gr. 1-40		
80 "		25–29	
81½ "		35–38	The slight rise only effect of a very strong current applied to a large, freshly-dissected nerve.
84 "			Artificial respiration stopped.
84¾ "		135–195	

Experiment XXXII.—A stout terrier. Artificial respiration, and woorari, in quantity sufficient to keep dog quiet and nearly to suspend respiration for a time, injected into the veins.

TIME.	DOSE.	PRESSURE.	REMARKS.
0 m.			Pneumogastrics cut.
5 "		90–100	Strong current applied to crural nerve.
5½ "		120–130	
15 "	gr. 1-40	65–75	Injected into peritoneal cavity.
24 "	gr. 1-40	60–70	Injected into peritoneal cavity.
38 "	gr. 1-40	45–55	Injected into femoral vein.
65 "		30–35	Strong current applied to crural nerve.
66 "		30–40	

These two experiments show that whilst the arterial pressure does rise when an afferent nerve is stimulated in a dog with divided pneumogastrics, after a dose sufficient gravely to imperil life, yet when artificial respiration is performed and very

large doses of the drug exhibited, the arterial pressure does not respond to the irritation of a sensitive nerve: *i.e.*, small doses of veratroidia do not affect very decidedly the vaso-motor system, but large amounts do exert a directly depressing influence upon these centres.

In concluding this investigation upon the action of veratroidia on the circulation, the results arrived at may be summed up in a few words.

The action of this alkaloid upon the circulation is altogether subordinate to its influence upon the respiration.

In minute doses it stimulates the cardiac inhibitory nerves or nerve-centres, but when given in sufficiently large doses it finally paralyzes the peripheral inhibitory cardiac nerves.

It exerts some action upon the heart-muscle or the contained ganglia; this action is probably a sedative one, but it is very feeble, and is only distinctly perceptible when the drug is precipitated at once upon the heart, or when the dose given is much above that required to arrest respiration. To kill the heart-muscle very large amounts are required.

Upon the vaso-motor system veratroidia acts as a depressant, but its influence is feeble, much less intense than its action upon the pneumogastrics. When artificial respiration is maintained, it can be given in such doses as to paralyze the vaso-motor centres.

PART II.—VIRIDIA.

Section A.—Action on the Circulation.

Mr. Mitchell announced some time since that he had found jervia in the root of veratrum viride. In a more recent, and as yet unpublished, investi-

gation, he failed to get what he was looking for, —the viridia of Bullock,—and was finally forced to conclude that his jervia was the same as the viridia of Bullock. After he had placed some of his jervia in my hands, my first experiments were directed to discovering whether this conclusion was true. Without giving these experiments in detail, it is allowable to state that the symptoms induced by his jervia were precisely those which I had seen caused by viridia. The same general quietness and weakness, the same peculiar trembling or muscular thrill ending in general convulsions, the same free salivation and absence of vomiting and of purging, were present in either case. In elaborate cardiometrical experiments the two alkaloids have also given identical results. I have no hesitation in asserting that they are one. As to the reason or cause of the asserted chemical differences I will not at present offer an opinion, but leave the Messrs. Bullock and Mitchell to settle it between them.

The general effect of viridia upon the circulation is well portrayed in the following experiments, which have been already published with more detail in the *American Journal of the Medical Sciences* for January, 1870.

Experiment XXXIII.—A moderate-sized cur.

TIME.	DOSE.	PULSE.	PRESSURE.	REMARKS.
0 m.			120–160	
5 "	gr. ½		120–160	Viridia injected into thigh.
15 "			120 (maximum.)	
20 "			65–95	
30 "		68	65–75	Dog quiet.
40 "	gr. ½			Injected into peritoneal cavity.
45 "			125	Convulsions.
50 "			75	Dog quiet.

Experiment XXXIV.—A stout Scotch terrier.

TIME.	DOSE.	PULSE.	PRESSURE.	REMARKS.
0 m.	gr. 1½	186	120–130	Hypodermically.
5 "			115–125	
10 "		160	110–120	
15 "		128		
20 "		80	85–105	Dog quiet.

These two experiments show that when viridia in suitable amount is given to a dog, the pulse as well as the blood-pressure falls very decidedly, without the production of marked symptoms other than general weakness. In order to confirm this, and at the same time to corroborate the opinion already expressed, that jervia and viridia are one thing, the following experiment was performed with some jervia obtained from Mr. Mitchell:

Experiment XXXV.—A stout slut.

TIME.	DOSE.	PULSE.	PRESSURE.	REMARKS.
				Injections into the femoral vein. The jervia very impure.
0 m.		135	105–120	
2 "		132	105–120	Dog breathing heavily.
2½ "	gr. 1-20			Doubtful how much went in.
4½ "		128	95–100	
6½ "	gr. 1-20	112	95–100	
7½ "		52	30–65	
8¾ "		76		
9¾ "		83	85–90	
10 "			95–105	
12 "		88	90–100	
15 "		112	100–110	
15¾ "	gr. ½			
19 "		90	70–75	
21 "		92	65–70	Dog very quiet.
22½ "		96	90–95	
24 "		92		
27 "	gr. 1-20		100–105	
28 "		72		
30 "		48	45–60	Dog quiet.
34 "			70–80	

TIME.	DOSE.	PULSE.	PRESSURE.	REMARKS.
35 m.			75–85	
36 "				Clot.
47½ "			85–90	When dog struggles, pressure rises to 100.
48¼ "	gr. 1-12.			Began to fall almost instantly.
49 "		84	50–60	
49½ "			55–65	
50½ "			70–75	
55 "	gr. 1-12		85–90	The dog has been struggling, to which the rise in pressure is probably due. Respiration is affected, but only in small degree.
58 "	gr. ¼			Clot.
66 "			100	Most violent, persistent convulsions have come on. The limbs shaking violently, all the muscles rigidly contracted. This, together with the violent respiratory efforts, drove the mercury up to 140, and even momentarily to 180.
				Tube has been placed in carotid.
73 "			60–75	The dog momentarily quiet.
74 "			110–125	Convulsions have again set in. There is no perceptible cardiac impulse.
76 "	gr. ¼		85	Dog still convulsed.
78 "		90	75–85	
81 "		132	75–80	
83 "				Clot. Respiration ceased. Heart found to be still pulsating; this continued for some time after entire arrest of respiration.

In comparing this experiment with those previously published, it must be borne in mind that in the last experiment the poison was thrown directly into the veins, and that therefore much more intense and especially more sudden effects are to be looked for; it should also be remembered that it is probable the specimens furnished by the Messrs. Bullock and by Mr. Mitchell were not of equal purity. Due allowance being made for these disturbing causes, I do not see how a close study of the records can fail to reveal

the identity of the two alkaloids. The great rise of pressure during the later periods of the last experiment was certainly owing entirely to the convulsions, the mercury in the cardiometer falling so soon as the muscles relaxed ; the phenomenon finds its counterpart in the first experiment with viridia.

Section B.—Action on the Heart and its Nerves.

In endeavoring to discover the exact method in which viridia lowers the pulse and blood-pressure, I first investigated its action upon the cardiac inhibitory system, and made the following experiments : those marked (V.) were performed some years since with Mr. Bullock's alkaloid ; the others were made with samples furnished by Mr. Mitchell.

Experiment XXXVI. (*V.*)—A small cur.

TIME.	DOSE.	PULSE.	PRESSURE.	REMARKS.
0 m.	gr. 1½	184	146–152	The pneumogastrics had been cut some time previously. Hypodermically given.
25 "		72	80–90	Pressure during struggles vibrates between 70 and 105.
30 "		80	65–95	Dog struggling some.
45 "		76	50–60	
60 "		68	38–60	

Experiment XXXVII. (*V.*)—A young mongrel.

TIME.	DOSE.	PULSE.	PRESSURE.	REMARKS.
0 m.		176	110–120	Par vagum already cut.
5 "	gr. 1			Given hypodermically.
20 "		164	110–115	
30 "		80	75–95	During struggles pressure falls to 70 and rises to 105.
40 "		76	65–85	
60 "		76	65–95	Constant convulsive tremors very marked; when they are especially violent the pressure rises to 110.

These experiments are sufficient to show that the reduction of the pulse produced by viridia is entirely independent of any action upon the cardiac inhibitory nerves. In order to determine whether large doses of the alkaloid paralyze the peripheral inhibitory cardiac nerves, further studies were required.

In two experiments, detailed below, the effect of galvanism upon the par vagum was therefore studied in a dog profoundly under the influence of the drug. An examination of the record of Experiment XXXVIII. will show that after the injection of a fifth of a grain of a very pure sample of the alkaloid into the veins, the cardiac inhibitory nerves were exceedingly sensitive to stimulus, and also that this sensitiveness was very slightly diminished by the further administration of nearly a grain and a half of the poison. In Experiment XXXIX. the amounts of the poison exhibited were very much less, but, as the animal was a very young pup, the effects of these doses were very marked,—arterial pressure falling to one-half its primitive height; yet the sensitiveness of the inhibitory apparatus was preserved intact. The first of the experiments seems to show that in enormous quantity the poison does slightly lessen the sensitiveness of the par vagum, but it is very possible that the diminution of sensibility alluded to may have been due to exposure of the nerves or some other accidental cause; at any rate, the experiments show that if viridia, even when given in enormous doses, has any action upon the cardiac inhibitory apparatus, such action is so slight that it may be practically disregarded. The experiments are as follows:

Experiment XXXVIII.—A stout dog. Spine cut.

TIME.	DOSE.	PULSE.	REMARKS.
0 m.	gr. 1-20	160	Into femoral vein.
10 "	gr. 1-10		Into femoral vein.
16 "		100	
17 "	gr. 1-20		Into a vein of the neck.
19½ "		92	
20 "		110	
21 "			One pneumogastric cut.
24 "		112	
32 "		108	Dog lost considerable blood.
32½ "			Cut remaining pneumogastric.
33 "		116	
38 "		116	A moderately strong current to par vagum caused immediate diastolic arrest.
42 "	gr. 1-10		Into jugular vein.
43 "		120	
43½ "	gr. ½		Into jugular vein. Immediate convulsions confined to the anterior part of the body.
47½ "	gr. ¾		Into carotid artery.
49 "		116	
51 "		116	Galvanic current of the same strength as before has a very decided effect on the heart, but does not completely arrest its movements.

Experiment XXXIX.—A small young pup. Woorari used, and spine and par vagum cut.

TIME.	DOSE.	PRESSURE.	REMARKS.
0 m.	gr. 1-10	95-105	
13 "	gr. ⅛		Into peritoneal cavity.
24 "		40-45	A mild current applied to par vagum caused immediate diastolic arrest.

It having been determined that neither the slowing of the pulse-rate nor the diminution of the arterial pressure produced by viridia is dependent upon an action of the poison upon the cardiac inhibitory apparatus, the question logically presents itself, whether the first of these phenomena is due to an action upon the accelerator cardiac nerves,

and the second to an influence upon the vaso-motor nerves, or whether both are the result of a direct influence upon the heart-muscle.

In order to determine whether the slowing of the pulse was independent of the accelerators of the heart, in the following experiment the attempt was made to divide the spine so high up as to paralyze these nerves, and in this way to eliminate their action from the problem. Unfortunately, at the post-mortem, care was not exercised to determine the exact point at which the spine was cut, and the single experiment is open to the objection that the supposed section of the accelerators was not anatomically proven to exist. As, however, the physiological result of such division was obtained, namely, a very slow pulse, such objection is perhaps more specious than valid. The experiment is as follows:

Experiment XL.—A terrier pup. Spine cut in lower cervical region. At the autopsy one lateral column found not to be completely crushed.

TIME.	DOSE.	PULSE.	REMARKS.
0 m.		96	Artificial respiration commenced.
3 "		82	
7 "	gr. ⅙		Into femoral vein.
23 "		80	
27 "		80	
34 "	gr. ⅓		Into peritoneal cavity.
35 "		68	
44 "		50	
46 "			Par vagum cut.
52½ "		48	

The record of this experiment proves that the reduction of the pulse-rate by viridia is independent of the nerve-centres. As a matter of course, when the pulse is already slowed by division of the accelerators, the fall is not so great after exhibition

of the alkaloid as in the uninjured animal. Yet, in spite of the division of the par vagum, the poison reduced the pulse to nearly one-half its original rate. The experiment does not, however, warrant the further deduction that the alkaloid has no action upon the accelerators, since it is evidently possible that an influence upon the nerves and upon the heart-muscle might be exerted simultaneously. The point must be left for future investigation; but I think the present light indicates that if viridia does act at all upon the accelerators, such action must be of minor importance.

The next point which logically offered itself for determination was whether the fall of the arterial pressure produced by jervia is due solely to an influence upon the vaso-motor nerves, or whether the poison lessens the working-power of the heart-muscle. In the following experiments a study was made of the effect of the drug upon the arterial pressure after paralysis of the vaso-motor nerves by section of the cord.

Experiment XLI.—A stout dog. Cord cut in the extreme upper dorsal region at 11.15 A.M.; observations commenced 11.25 A.M.; the jervia employed containing a good deal of resin.

TIME.	DOSE.	PULSE.	PRESSURE.	REMARKS.
0 m.			90–100	Artificial respiration commenced.
1 "			80–85	
4 "	gr. 1-20	160	75–85	Into femoral vein.
5 "		135	80–90	
7 "	gr. 1-20		80–90	Into femoral vein.
8 "		140	80–90	
9 "			75–80	
10 "		120	60–70	
11 "		120	50–55	
12 "			50–60	

TIME.	DOSE.	PULSE.	PRESSURE.	REMARKS.
14 m.	gr. 1-10		60–65	Into femoral.
15 "			60–65	
17 "		120	65–70	
20 "		100	55–60	There appears to be a clot in the femoral vein interfering with passage of alkaloid into the circulation.
21 "	gr. 1-20			Into vein in neck.
21½ "		108	45–50	
22 "		116	50–75	
22½ "	gr. 1-10			Into jugular vein.
23 "			40–45	
23½ "		92	45–50	
24 "		110	40–50	
39 "		116	30–35	Pneumogastrics cut a few minutes since. Dog has lost some blood.
42 "		116	50–55	
46 "	gr. 1-10		50–55	Into jugular.
47 "		120	50–55	
47½ "	gr. ½			Into jugular.
48½ "			45–50	
51½ "	gr. ¾			Into carotid.
52 "			35–40	
53 "		116	35–40	
55 "		116	35–45	
61 "	gr. ½			Into jugular. Violent convulsions at once confined to the anterior part of the body.
63 "		120	30–35	
65 "		112	35–40	Galvanization of spine caused a general convulsion of a mild type, with a rise of the blood-current to 70 or 80, the pulse instantly becoming exceedingly rapid. On withdrawing the poles, the mercury fell at once, in half a minute standing about 40,—the pulse being 208.

Experiment XLII.—A terrier pup. Cord divided in lower cervical region. At the autopsy one lateral column found not to be completely mashed.

TIME.	DOSE.	PULSE.	PRESSURE.	REMARKS.
0 m.	.	96	100–135	Artificial respiration resorted to at end of first minute.
2 "			95–100	
3 "		82	100–105	
7 "	gr. ⅙		115–125	Into femoral vein.
9 "				Convulsions in anterior part of the animal.
30 "			55–75	Artificial respiration very active.
34 "	gr. ⅓			Into peritoneal cavity.
35 "	.	68	115–125	Convulsive rigors and tremblings in anterior part of body very marked, and, to some extent, in one-half of posterior portion.
44 "		72	115–120	
46 "				Par vagum cut.
52 "			75–85	Dog quiet.

These two experiments, in conjunction with what has been previously brought forward, certainly prove that jervia exerts a direct influence upon the cardiac muscle, lessening not only the rapidity but also the force of its pulsation.

In Experiment XLI. the pressure was reduced to a little more than a third of its primitive amount, and in Experiment XLII. a similar but less decided fall was seen. The temporary rise of the blood-pressure which occurred late in Experiment XLII. was undoubtedly due simply to the general muscular contractions.

In order to investigate still further, and determine more positively, the action of viridia upon the cardiac muscle, the following experiments were performed upon batrachians:

Experiment XLIII.—A rather large frog. The spine cut just below the head, and the heart laid bare. Two

minute drops of a solution of jervia (three grains to the fluidrachm) were dropped upon the heart, which had been beating at the rate of eighty per minute. Instantly motion ceased, but in a few seconds re-commenced, and a minute afterwards the pulsations were sixty per minute. Shortly after this a little of the solution was injected into the heart, when movement ceased at once, and only occurred again in the form of a few imperfect, distant pulsations. There was a not very well marked apical white spot, and the ventricles refused entirely to respond to mechanical stimuli. Movements of the mouth, apparently voluntary, continued some minutes after the cardiac arrest.

Experiment XLIV.—A moderate-sized frog. A few drops of the solution were thrown into the cardiac region. In a minute afterwards, voluntary motion not being markedly affected, the heart was exposed, and found to be beating twelve times a minute. About a half-minute after exposure, all spontaneous cardiac movements ceased, the heart continuing to respond to mechanical stimuli, and retaining this power for some minutes. Three minutes after the cardiac arrest, the frog made three rapid, successive, vigorous jumps.

Experiment XLV.—A frog of moderate size. About ten minims of the solution were injected into the pericardial space. Three-fourths of a minute, voluntary movements vigorous; one minute, spontaneous cardiac movements cease; two minutes, heart does not respond at all to mechanical stimulus; three minutes, feeble movements apparently voluntary; four minutes, frog sits up and opens his eyes widely, and when the balls are touched with a pencil the membranes respond, although somewhat sluggishly.

In the first of these experiments the effect of the direct application of the drug to the heart was very apparent. In the last two experiments the intention was, if possible, to paralyze the heart before the drug was carried freely into the general circulation. In this I was only partially successful, although voluntary movement persisted in a greater or less degree after complete arrest of the heart.

Certainly, however, these experiments are confirmatory of those made upon warm-blooded animals, and show that viridia does act upon the heart itself.

Section C.—Action on the Vaso-Motor Nerves.

It is, of course, a matter of a good deal of interest and importance to determine whether viridia exerts an influence upon the vaso-motor nerves. It has already been shown that it lowers the arterial pressure by a direct action upon the heart; but this, of course, does not prove that it has no power over the blood-vessels, since it is very possible for the alkaloid to have a double action, affecting both the heart and the vaso-motor centres. It is evident, however, that the cardiac influence of the alkaloid must so mask any action upon the vaso-motor centres which it may exert as to render the proof of such action difficult.

In the following experiment the effect upon the blood-pressure of stimulating a sensitive nerve was taken advantage of to determine the point at issue:

Experiment XLVI.—A pup. Par vagum cut. Woorari administered so as to cause complete paralysis, and the dog kept alive by artificial respiration.

TIME.	DOSE.	PRESSURE.	REMARKS.
0 m.		95–115	A mild current applied to exposed femoral nerve.
½ "		160–170	Current broken.
4 "	gr. 1-10	95–105	Into femoral vein.
6 "		80–100	Current previously employed.
8 "		136	Maximum reached. Current broken.
16 "		40–50	
17 "	gr. ⅙		Into peritoneal cavity.
19 "		35–45	
25 "		40–45	Current of strength previously used applied to a freshly dissected axillary nerve.

TIME.	DOSE.	PRESSURE.	REMARKS.
25¼ m.		55–60	
26 "		40–45	Current broken.
29 "		20–25	Curent applied to brachial nerve.
29½ "		30–35	Current broken.
30 "			
38 "			A mild current applied to pneumogastrics caused instantaneous diastolic arrest of the heart.
39 "		25–30	An intense current applied to a freshly dissected brachial nerve, on side opposite to that before used.
40 "		25–30	Current removed from brachial and applied to previously unused femoral.
41 "		25–30	Current broken.
43 "		25–30	Artificial respiration stopped.*
43¼ "		20–25	
43¾ "		15–20	
44¼ "		10–15	
45 "		9–12	Cardiometer removed.

Experiment XLVII.—A stout cur.

TIME.	DOSE.	PRESSURE.	REMARKS.
0 m.		85–90	Par vagum cut, and woorari, in small amount, given.
3½ "			Galvanism to femoral nerve caused some struggles.
4 "		100–140	Current broken.
6 "	gr. ¼	90–95	Injected into a vein ; clot in latter so impeded progress that it is very doubtful whether any of the alkaloid got into the circulation.
13 "		90–103	
15 "		85–90	Galvanism as before.
15¾ "		110–140	Current broken.
18½ "	gr. ¼		Into vein ; instantly struggles commenced, soon passing into violent convulsions, *not* preceded by any fall of the arterial pressure.
21½ "		160–165	Still convulsions. One-half grain of woorari.
26 "		75–80	Dog quiet.
28 "		65–70	

* This experiment compared with Experiment XXVI. shows the great difference between the action of the two alkaloids upon the heart, in that in viridia-poisoning an excess of carbonic acid in the blood is powerless to elevate the pressure in the arteries.

TIME.	DOSE.	PRESSURE.	REMARKS.
30 m.			Violent convulsions, during which the mercury in the cardiometer rose and fell incessantly, reaching 185.
31 "		60	Dog quiet.
32¼ "		50–55	More woorari given.
34 "			Mild current to par vagum acted very decidedly on the heart.
46½ "	gr. 1		Instantly violent convulsions as before, not preceded by a fall of pressure.
46¾ "		145	
51 "		80	Dog quiet.
52 "		65	
60 "		55–60	Current applied to a fresh femoral nerve.
60½ "		85–90	
60¾ "		75–80	Current broken.
64 "	gr. ½		Injected.
76 "		40–50	
80 "		40–45	An intense current applied to a freshly exposed brachial nerve.
80¼ "		50	
81 "		50–55	
83 "		65	After this the mercury began to fall steadily, in spite of the continuous application of the current to the nerve.

In reviewing these experiments it will be found that in the first (Experiment XLVI.) a tenth of a grain was sufficient to affect decidedly the response of the circulation to the irritation of a sensitive nerve. The arterial pressure had only been lowered fifteen measures, yet a current applied as before the injection raised the column only to one hundred and thirty-five instead of one hundred and sixty. When a sixth of a grain more of the poison had been exhibited, the rise produced by currents applied to the largest freshly-dissected nerves had scarcely any effect, and finally failed altogether, at a time, too, when the heart responded most readily to stimulation of the pneumogastrics.*

* I am very doubtful, however, whether a dose was not given about the twenty-seventh minute in Experiment XLVI. and omitted by mistake from the record.

In the second experiment, either because the drug used was less pure or the animal less susceptible, larger doses were required to effect the destruction of the reflex vaso-motor activity. It is, of course, possible that viridia paralyzes the afferent or sensitive nerves and thereby prevents the impulse being carried to the vaso-motor centre; but, as the animals show evident signs of pain when the nerve is irritated in viridia-poisoning, the two experiments seem to me to prove that viridia is a vaso-motor as well as a cardiac depressant.

In summing up the present study of viridia, the results obtained may be put in a very few words, as follows:

Viridia in its action upon the circulation, as compared with its influence upon the respiration, is very much more powerful than veratroidia. The slowing of the pulse and the lowering of the arterial pressure caused by viridia are due to a direct action upon the cardiac muscles and upon the vaso-motor centres, upon both of which the alkaloid acts as a powerful depressant; upon the inhibitory and accelerator nerves of the heart, viridia acts not at all, or so slightly that its influence is not perceptible.

As has already been stated, Mr. Mitchell affirms that chemically there is no difference between viridia and the older alkaloid of veratrum album jervia. It is a matter of interest to test his conclusion physiologically, but, unfortunately, he has only been able to furnish me with sufficient of the veratrum album jervia to make a single experiment, as follows:

Experiment XLVIII.—Acetate of jervia from veratrum album in alcoholic solution. A stout cur; the cord cut in the upper dorsal region at 11.30 A.M. The first cardiometrical observation taken at 12 noon.

TIME.	DOSE.	PULSE.	PRESSURE.	REMARKS.
0 m.		186	65–75	
4 "			70–80	
5½ "	gr. ¼		80–90	Injected into femoral vein.
6½ "			70–80	
6¾ "		150	65–75	
7 "			60–70	
8 "			70–80	Dog trembling slightly.
9 "			70–85	
10 "	gr. 1-30	165	75–85	Into femoral vein.
10¼ "			55–65	
11 "		93	35–45	
12 "		102	40–50	
15 "		105	45–55	
18 "		108	60–70	
19¼ "	gr. 1-30			Into femoral vein.
19½ "			50–55	
20 "		96	40–45	
21 "		99	45–50	
22 "				Pneumogastrics cut.
22½ "		183	70–80	
23 "			60–68	
24 "		180		
25¼ "	gr. 1-30		65–75	Into femoral vein.
26½ "		150	57–70	
32 "		126	60–70	
34½ "	gr. 1-15			Into femoral vein.
37 "		150	50–55	
40 "		150	50–55	A slight flow of saliva; it is possibly due to heat and to gag.
42¼ "			50–60	
43 "	gr. 2-15			Into femoral vein.
44 "				A struggle; doubtful how much voluntary; it may be convulsive. Commenced in upper part of body and there confined, before the blood-pressure was affected by injection.
45 "		144	35–40	
46 "		126	45–50	
48 "		156 very irregular	30–35	Galvanization of par vagum caused instant arrest of heart.
51 "	gr. 2-15			
53 "				A clot is in veins, and it is doubtful as to how much of remedy penetrated.
60 "	gr. ¼			Into opposite femoral.

TIME.	DOSE.	PULSE.	PRESSURE.	REMARKS.
61 m.			15–20	Cannot count pulsations. Finger inserted through an opening in chest and brought into contact showed a pulse of 165.
62 "	gr. ½			Galvanization of pneumogastrics arrests heart.
63 "		210		Counted as before.
70 "	gr. ¼			Injected directly into heart.
75 "	gr. ⅓			Injected into a large vein in neck.
78 "		64		Motions of heart very weak to finger.
80 "				Cardiac pulsations ceased. Heart does not respond at all to strongest currents. The intestines in active motion, and respond well. Voluntary muscles respond well. The dog has not had violent convulsions at any time. During last half-hour has been perfectly quiet.

At the time this experiment was made, I thought more of the veratrum album jervia would be forthcoming, or otherwise the character of the experiment would have been different. In examining the record it will be seen that the drug produced a steady fall of the arterial pressure and lowering of the pulse-rate up to the time when the pneumogastrics were cut, whereby the pulse was greatly accelerated. After the division of the inhibitory nerves the continuous exhibition of large doses failed to affect the pulse, although the pressure fell very decidedly, even, at last, to zero. When the arterial pressure was almost at a minimum, the pneumogastrics were still sensitive to galvanic currents. Finally the heart was arrested, and its muscle was unable to respond to the strongest stimuli. As the reduction of the arterial pressure occurred after division of the spine, *i.e.*, paralysis of the vaso-

motor system, it obviously was the result of a direct action upon the cardiac muscle. Making the obvious deductions from these facts, the above experiment would seem to indicate that jervia of veratrum album acts first as a stimulant to the cardiac inhibitory nerves, slowing the pulse through them, and that after their section it reduces the force but not the number of the cardiac pulsations.

If this be so, the alkaloids of V. album and V. viride are not the same, and Mr. Bullock is right. The conclusion cannot, however, be accepted as proven, since with the jervia was injected a quantity of alcohol, and it is possible that after section of the pneumogastrics this alcohol may have increased the rate of the cardiac pulsations. On the other hand, the convulsions caused by the true jervia were not nearly so violent as those ordinarily seen with viridia. So that, whilst confirmation is needed before any positive opinion can be reached, the evidence thus far points to the distinctness of the two alkaloids.

PART III.—GENERAL CONSIDERATIONS.

Having an intimate knowledge of the action upon the circulation of the only two active principles of veratrum viride, it would seem an easy task to determine the effect of the drug. Unfortunately, however, the exact proportion in which the alkaloids exist in the root is not known. Mr. Bullock obtained the viridia much more abundantly than the veratroidia, but Mr. Mitchell found the former alkaloid the least plentiful. Neither of these investigators claims that he obtained more than a portion of the active principles in the roots which he worked with, so that the question as to which alkaloid is most abundant seems doubly unsolved. It appears to me probable that the viridia is the

more abundant, because in veratrum viride poisoning the circulation is affected so very much more intensely than the respiration.

Be these things as they may, it is plain that in those actions in which the two alkaloids agree, the crude drug will have most power, and, *vice versa*, if in any influences the two alkaloids are antagonistic, in such influences the veratrum viride will be least powerful. In what points, then, do the two alkaloids agree? Evidently in two,—namely, their depressing influence upon the force of the cardiac muscle, and upon the vaso-motor nerves.

Veratroidia lowers the pulse-rate by its action upon the inhibitory centres; viridia lowers the pulse-rate by benumbing, as it were, the muscle. These actions are not the same; it is even conceivable that they may to some degree be antagonistic, or, in other words, that a benumbed heart-muscle may not respond as quickly as normal to an inhibitory impulse. Any one who has used veratrum viride habitually must have noticed, more or less frequently, good effect produced by it before the pulse-rate was materially diminished. This, it seems to me, is explained by the above considerations, the arterial pressure being affected before the pulse-rate.

Although it might seem fitting to discuss the clinical uses of veratrum viride at length, yet I will refrain from so doing, for several reasons. In the first place, there is very little that is actually new to be said; in the second place, my own opinions have been sufficiently expressed elsewhere; in the third place, any doctor knowing the physiological action of this drug ought to be able to apply such knowledge to the treatment of disease. The practical value of the present study is in rendering clear and definite the clinical employment of the drug rather than in

opening any new uses for it. It has been over and over again distinctly stated that the action of veratrum viride is that of a pure depressant. Yet its use in various *asthenic* diseases is still from time to time recommended in the journals. It hardly seems necessary to stigmatize such practice as irrational and harmful. To weaken still further an already weak and struggling heart because the pulse-rate is high is simply murderous.

Before closing this article, I desire to call attention to the great similarity between many of the effects of veratrum viride and of depletion. If one-third of the circulatory fluid is withdrawn by bleeding, of course the inflamed part is more or less starved. Veratrum viride really withdraws the circulating fluid from the inflamed part almost as directly as does venesection. The capillaries of the inflamed tissue are distended, and the blood rushes to and accumulates in the part largely because the capillaries are thus distended. Under the influence of the veratrum the general rapidity of the blood-current is lessened, and of course the inflamed tissue feels this in its blood-supply; but, more than this, all the capillaries of the body are enlarged, and, claiming their share of the vital fluid, withdraw it from the inflamed part. If the average increase of the vessels should amount to one-third their original calibre, an effect in some degree similar to that produced by the removal through a vein of one-third of the blood ought to be obtained for the time being.

The extraordinary value of the drug in many sthenic conditions probably no one who has used it with cautious boldness will deny, and with our present light the *rationale* of its action seems very clear.